Am. J. Trop. Med. Hyg., 54(5), 1996, pp. 439–442

TROPICAL DISEASES: NEW PERIL, NEW PROMISE*

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After thinking about the subject of this presidential address for a significant period of time, I have chosen to discuss a view of the current state of tropical medicine and have titled this Tropical Diseases: New Peril, New Promise. I would like to view our field in the context of the expansion of medical research during the past half-century and the changes which the scientific enterprise is now undergoing. Regardless of whether we are employed by an educational institution, the military, or a U.S. government agency or are in the process of receiving graduate or postgraduate training, we are all trying to adjust from an expanding research enterprise to a steady state system. While the individual issues may be unique, the underlying theme is common to us all.

To gain perspective on the current situation, let us go back to 1945 and begin with Vannevar Bush's report to President Truman, a document which has come to be known as "Science: The Endless Frontier".[1] This was a far-reaching and visionary statement that laid the groundwork for federal support of science and the growth of the research university for the past 50 years. This important document fell into relative obscurity, but has recently been re-examined in the light of the end of the Cold War and the changes in the scientific enterprise over the past 50 years.

Vannevar Bush headed the Office of Scientific Research and Development under Franklin Roosevelt during the second World War. He was the nation's "science czar". With the war drawing to a close, he was asked by President Roosevelt to address the role of scientific research and development in postwar society, and he approached the same questions we are faced with today: the impact of science on the national economy, the role of government in assisting research, and the development and training of American scientists. His far-reaching report and its implementation set the course for the partnership between scientists, universities, and the federal government and the transformation of science in the United States in the ensuing 50 years.

In looking into this report, I discovered that Vannevar Bush even addressed parasitology, stating that "malaria has been controlled" due to the use of DDT as an example of the success of the scientific effort. Although "Science: The Endless Frontier" was visionary and influential in many ways, Vannevar Bush and others of the time clearly underestimated the genetic plasticity of microorganisms and their vectors. Nor could he have foreseen the emergence and spread of chloroquine-resistant *Plasmodium falciparum* and now, in some areas, *Plasmodium vivax*. We are all aware of similar stories with bacteria such as the emergence of drug-resistant *Mycobacterium tuberculosis* and the emergence of new virulent types of viruses such as the human immunodeficiency virus (HIV).

Vannevar Bush could also not have foreseen the tremendous changes visited on this planet since the end of World War II, mostly as a result of human activity, that have promoted the spread of disease and altered the balance between humans and the environment. As an example, the mining activity in the Amazon Basin and the clearance of the rain forest have altered the ecology of the region and promoted the spread of diseases such as malaria. There are many other examples of irrigation and hydroelectric projects that have increased the spread of diseases such as schistosomiasis. We need only to look in the popular press to find additional examples of changes in the interaction of microorganisms and the human species -hantavirus in the southwestern United States and elsewhere, Ebola virus in Africa, concerns about the spread of dengue virus in Latin America and possibly to the United States, most recently an outbreak in Nicaragua of what may be leptospirosis, and of course AIDS. Yet these examples, which are highly visible in the press, do not begin to encompass or address the magnitude of chronic infections with some of the microbes we are studying.

The enormous expansion of medical science and research since the end of the second World War is now being reexamined with the end of the Cold War because 1) the scientific enterprise cannot be an infinitely expanding system; 2) there are differing views of the appropriate roles of the federal government in our society; and 3) our society has not been able to come to grips with a variety of serious social and economic problems. This conflict is currently being acted out, most vividly just prior to the ASTMH annual meeting, when the federal government ground to a halt as a continuing resolution came to an end and battles between the Republican-controlled Congress and the Democratic President escalated to a stand-off. As a result, many of our members were unable to attend the annual meeting of our society.

There can be no doubt as to the growth of the scientific enterprise. The growth rate of biomedical researchers has been 10 times that of the overall work force in this country. This has been fueled by significant increases in the National Institutes of Health (NIH) budget from $43 million in 1950 to more than $11 billion in 1995.[2] Our own field has experienced a parallel expansion in funding. However, it is important to note that the years 1993–1995 have shown essentially no growth in the total NIH budget when viewed as constant dollars. Moreover, some budget proposals put forward this year would actually cut the NIH budget between now and the year 2002.

Now the scientific enterprise is being reexamined and the rate of real growth has diminished, so that we are all entering a steady state era. Dr. Harold Varmus, Director of the NIH, recently titled his Shattuck lecture *Biomedical Research Enters the Steady State*.[2] Our challenge will be to sustain our own enterprise and the world's most successful science and

*Presidential Address given before the 44th Annual Meeting of the American Society of Tropical Medicine and Hygiene, San Antonio, Texas, November 19, 1995.

technology enterprise in an era of steady state economics and perhaps even contraction.

Currently, academic institutions, industry, and government are simultaneously experiencing enormous changes. Let us look at some of the pressures facing these institutions. First is the federal budget and attending deficits. Attempts to reduce the deficit and stem projected budget increases, including those due to rising health care costs (now 14% of the GNP), have led to cuts in health-related activities. This was vividly brought home to me earlier this year when I represented the ASTMH and gave testimony before the House Appropriations Sub-Committee chaired by Representative Porter of Illinois. I was there to support the NIH budget, the Centers for Disease Control and Prevention (CDC) emerging infections program, and other international health activities. The speaker before me represented the American Psychological Association and behavioral research. After he completed his testimony, a new representative on the Sub-Committee said, "Doctor, do you realize that this government is in deficit? I want you to tell me where to cut the federal budget by 25%".

There are also new realities facing academic health centers, especially due to reductions in reimbursements for clinical care and the necessity to compete with other health care providers for contracts from managed care organizations. In the past, practice plan funds have been a significant support to biomedical research. In 1992–1993, the research contribution from practice plans was $820 million.[3] Decreases in reimbursement reduce the capacity of academic medical centers to subsidize other activities such as research. Schools of medicine have become dependent on clinical practice revenue -currently 40% of the income at medical schools nationwide. Now the need to provide service is changing the structure of these institutions. Many schools are shifting their focus to primary care so they can compete successfully for contracts from managed care organizations such as health maintenance organizations (HMOs). This situation is exacerbated by the fact that teaching hospitals are responsible for more than half of the uncompensated medical care in the U.S. As a result, clinicians are pressured to deliver high-quality medical care, teach medical students, residents, and fellows, and still conduct scholarly activity. Basic scientists are pressured to fund their research and their salaries, do high-quality teaching, and perform other service activities. Other institutions of higher education are also experiencing budget squeezes. Overall, educational institutions, government agencies, and industries are all facing constrained budgets and expectations to do more with less.

What is the situation for those who are graduate students or are in postdoctoral programs? The Committee on Science, Engineering and Public Policy of the National Academy of Sciences recently made a major study of this issue.[4] Let us look at the current realities.

- The average time to complete a doctoral degree has increased in all fields -for the life sciences from 5.2 years in 1962 to 6.7 years in 1992.
- The total number of students receiving Ph.D. degrees increased from 18,000 per year in the 1976–1986 period to 25,000 in 1993.
- The postdoctoral population has increased faster than the graduate student population -a 64% increase from 1982 to 1992 versus a 27% increase in the graduate student population during the same period.
- The percentage of young biologists less than 36 years of age who applied to NIH for any type of support fell by 54% from 1985 to 1993. This may reflect the fact that fewer are in a position of independence which would enable them to apply.
- More Ph.D.'s are finding employment outside the university system, particularly in the corporate sector. More than half of Ph.D.'s now go on to nonacademic jobs so that graduate students must be prepared for a variety of careers in addition to research.
- The oversupply of Ph.D.'s relative to the number of academic opportunities appears to be growing, leading to frustration with the current system. It appears to many that there is a line forming in front of any open tenure track position, which is of concern to graduate and postdoctoral students. This is illustrated by a recent issue of *Science,*[5] which included a major section on careers and highlighted the uncertainties of many of our trainees. As another example, a recent editorial in the *Journal of NIH Research* titled "Higher Education is not a Job Training Program"[6] elicited some heated responses from readers anxious about job prospects after years of graduate training.

Given this situation, we have to recognize that we must encourage breadth and flexibility in training of graduate students because the opportunities of the future will favor such individuals regardless of their eventual professional employment. The challenge for us as a society is to make our field attractive for young investigators.

How can this be accomplished, given that most support for graduate training comes from faculty research grants that have goals and objectives which must be achieved as a basis for future funding? How can we encourage breadth and flexibility and still provide funding for our trainees? One mechanism might be the development of new types of training grants that will place a premium on the types of opportunities that graduate students experience, with an emphasis on interdisciplinary education and rotations through off-campus sites -e.g., a field site or a biotechnology company or a government laboratory like the CDC. Perhaps this should be considered as an important selection criterion for recipients of NIH training programs in tropical disease research in the future. Another aspect of graduate education should involve developing the communication skills of our trainees. Some institutions are initiating courses designed to teach students how to present a lecture or lead a small discussion group. Such skills will serve students well regardless of their eventual vocation.

Our field has the capacity to encompass many different aspects of biology as well as the application of basic studies to real-life situations relating to human health, and it is very exciting and attractive in this regard. It is particularly well-suited to interdisciplinary training with an international flavor and can be a model for the training programs of the future. The number of nations represented here as recipients of our Society's travel awards is impressive, as is hearing about the mobilization of resources and technologies that have recently been brought to bear in a short time frame in response to various outbreaks of infectious diseases around the globe.

As additional assistance, we should use new information technologies to assist our students and trainees. The ASTMH is exploring new information technologies including the Internet. In that process, we should place emphasis on communicating with trainees both nationally and internationally as an important goal. New opportunities in global communication will allow us to keep in touch with our graduates regardless of their location and provide services for them such as information about employment and research opportunities.

Given the current situation, changes in academic centers and in government agencies will be required. How should we adapt to the new realities of our professional lives? Some feel that radical changes are required (reinventing government or reinventing the university), while others hold the view that more minor modifications will suffice (reengineering government or the university). On whatever scale, change will not be easy because change is never easy and because both government and universities have become large, complex organizations, in many ways big businesses.

To compensate for declining revenues, academic centers and research institutes have sought nongovernmental sources of funds, including income from biotechnology or pharmaceutical industries. As another alternative, the Medical Research Fund bill, introduced by Senators Harkin and Hatfield last year and included in all of the major health reform bills, would have provided a nongovernmental source of revenue derived from a trust funded by a small surcharge on health insurance. While this bill was not enacted last year due to the failure to pass health care legislation, it will be reintroduced in Congress in a slightly different form, with revenue deriving instead from a levy on tobacco products.

Despite attempts to identify alternate sources of income, major issues of efficiency, accountability, and productivity will need to be addressed. We must look for new ways of doing things. New types of interactions will be required. For example, what role is there for the "virtual" university? Rapid technological changes have increasingly made possible the integration of text, sound, and visual images that can be available anywhere on the globe. New communication linkages can in some ways remove geographic barriers to participation in classes. Off-site students -both national and international -can now be included in the class. Can we develop "virtual courses" in various aspects of tropical diseases which would be given on line?

New paradigms will also be required for scholarly investigation as well. The European Economic Community has developed mechanisms to promote partnerships among their members and developing countries for tropical disease investigations. Some of us are discussing the possibilities of a "virtual center" to network malaria investigators in order to share information, ideas, reagents, etc., and consequently maximize scarce resources. Our society welcomes and encourages national and international collaborations and interactions. Collectively, we have a great deal of experience in conducting collaborative research and development on an international scale. Consequently, we have the opportunity to take the lead in exploring new types of scientific interactions and relationships between academic institutions, government agencies, and the private sector. We need imaginative approaches and the will to carry them out.

We also need new methods for international alliances and partnerships. As we all recognize, the distinction between domestic and international health is outmoded. We need an infrastructure to permit surveillance on a global level and ASTMH has supported the efforts of the CDC and the Fogarty Center to increase monitoring, investigation, and control of emerging and re-emerging infections.

Overall, these thoughts can be summarized in "watchwords", as recently suggested by Kumar Patel.[7] While the watchwords of the past have included things like grant income, expanding laboratory space, building new research buildings, tenure, and investigator autonomy, those of the future are likely to have more to do with teamwork, coordination, communication, and multidisciplinary collaboration on a national and international scale.

Finally, we must articulate a rationale for our activities to the public and to our elected representatives to make the case that our work is coupled to national needs and that it merits a stable funding base. Surveys show that the public is very supportive of biomedical research, more so than for other types of scientific endeavors. In terms of a justification for biomedical research, I would like to cite the Speaker of the House of Representatives, Mr. Newt Gingrich. Mr. Gingrich has a view of biotechnology as fueling economic growth into the next century. For example, he has stated that "If we move aggressively, biotechnology will be the prototypical 21st century growth industry, strengthening America's trade balance and creating the highest-quality, best-paying jobs in the world".[8,9] Mr. Gingrich has probably come to this view because he has looked at the data. In 1993, the biotechnology enterprise included more than 1,300 small and medium-sized companies providing 103,000 jobs and a market value of $41 billion.[10] In addition, the United States pharmaceutical industry employed 350,000 people in 1993 and generated a trade surplus of $1.4 billion. This has also benefited academic institutions. For example, the top 35 research institutions obtained 1,063 patents from 1989 to 1990, and the majority were licensed yielding $113 million in income. Such partnerships with industry are likely to increase in the future and probably will take new forms.

Mr. Gingrich is also no doubt aware of recent attempts to provide a quantitative assessment of the economic impact of research and development. Laura Tyson, chairperson of the President's Council of Economic Advisers, has reported that the average rate of return on private investment in research and development is 20–30%. Additional considerations suggest that the rate of return on private investment may be closer to 50%. She believes that the return on federal research investment may be as much as 150%.[2] These numbers might be compared with investment in a new factory, which provides a return of 6–7%. Leaders of industry also recognize the economic value of investment in research, as exemplified by the fact that a number of them took out an advertisement in the *Washington Post* earlier this year to urge Congress to look favorably on such appropriations.

At times, it is more difficult to make the case for diseases that are not prevalent here in the United States, and partnership with the biotechnology enterprise is less obvious for new antimalarial drugs than it is for new chemotherapeutic approaches to cancer or osteoporosis. Yet the World Bank calculates that the Disability Adjusted Life Years (DALYs))

lost due to malaria in the world exceed those for cancer or hypertension. We need additional data in this regard. For example, a recent report indicated that the value of stock exchanges in the developing world has risen 11-fold in the 1985–1994 period, but only four-fold in the developed world for the comparable period.[11] What is the impact of disease control on population stabilization, economic development, and international security?

Today there is enormous potential for discovery in the study of parasitic diseases. Regardless of whether one considers new attempts to transfect genes into recalcitrant malaria parasites or whether one is making new observations on the importance of bed nets in reducing child morbidity and mortality from malaria, the organisms we study are interesting and exciting from many points of view. First, they are illustrators of new biological paradigms, e.g., RNA editing in kinetoplastids is now seen in other species as well. Second, these organisms are useful probes of basic cellular processes, e.g., *Leishmania* and schistosomes have provided insights into T cell differentiation and cytokine production and this knowledge has been applied to a variety of infectious and inflammatory diseases. Finally, these organisms and their vectors are fascinating and important biological entities for humankind. They must be understood on a biological level both in the laboratory and in the field. I would like to cite the recent dramatic advances that have occurred in understanding the molecular and biological basis of pathogenesis in a number of bacterial and viral systems. As an illustration of a new perspective on bacterial pathogenesis, let me use the view of *Listeria* provided by the work of Tilney and Portnoy. Their elegant work has revealed that these intracellular bacteria utilize host cell molecules to travel through the cytoplasm and be taken up by another cell without contacting the external environment.[12] Many of the organisms we study are more complex eukaryotes, and we have the potential to develop a similar biological understanding of pathogenesis over the next decade. This is a necessity if we are to seek new intervention strategies for these important diseases.

To make these advances we must emphasize the critical importance of cross-fertilization between disciplines -microbiology, molecular biology, immunology, cell biology, pathology, and public health. The ASTMH must provide that umbrella and be the catalyst for such broad, multidisciplinary interactions. The result will be a livelier, richer, and more productive field for us all.

Let me conclude with a quotation from Vannevar Bush's report with an observation which is as true today as it was in 1945: "Science by itself provides no panacea for individual, social, and economic ills. It can be effective in the national welfare only as a member of a team. . . But without scientific progress no amount of achievement in other directions can insure our health, prosperity and security as a nation in the modern world."[1]

Acknowledgments: This presentation is dedicated to the memory of my parents, Thomas and Florence Long, for their continual support and encouragement. I would like to acknowledge the students and postdoctoral fellows who have contributed to my laboratory, as well as Thomas Daly who has worked with me as a Research Associate for many years. I would also like to acknowledge my current colleague, Dr. Akhil Vaidya, for continual discussions and my former colleague, Dr. William Weidanz, who sparked my interest in malaria parasites. Special thanks is due Dr. Dyann Wirth for helpful comments on this presentation.

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